(7) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[39 FR 19145, May 30, 1974, as amended at 50 FR 19920, May 13, 1985]

Subpart B [Reserved]

Subpart C—Injectable Dosage Forms

§ 450.210 Sterile bleomycin sulfate.

The requirements for certification and the tests and methods of assay for sterile bleomycin sulfate packaged for dispensing are described in § 450.10a.

[40 FR 52006, Nov. 7, 1975]

§ 450.220 Dactinomycin for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Dactinomycin for injection is a dry mixture of dactinomycin and mannitol. Each container contains 0.5 milligram of dactinomycin. Its dactinomycin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of dactinomycin that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 4.0 percent. Its pH is not less than 5.5 and not more than 7.5. The dactinomycin used conforms to the standards prescribed by § 450.20(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter, and in addition each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container the statement ''Protect from light and excessive heat''.

(ii) On the outside wrapper or container and the immediate container the statement ''For hospitalized patients only''.

(3) *Requests for certification; samples.* In addition to the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The dactinomycin used in making the batch for dactinomycin content, loss on drying, absorptivity, crystallinity, and identity.

(*b*) The batch for dactinomycin content, sterility, pyrogens, loss on drying, and pH.

(ii) Samples required:

(*a*) The dactinomycin used in making the batch: 10 containers each containing not less than 40 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 20 immediate containers.

(*2*) For sterility testing: 20 immediate containers.

(b) *Tests and methods of assay.* Dactinomycin is toxic and corrosive. It must be handled with care in the laboratory. Transfer all dry powders in a suitable hood, while wearing rubber gloves. Avoid inhaling fine particles of the powder. Do not pipette by mouth. If any of the substance contacts the skin, wash copiously with soap and water. Dispose of all waste material by dilution with large volumes of trisodium phosphate solution.

(1) *Dactinomycin content.* Proceed as directed in § 436.331 of this chapter, except prepare the sample solution and calculate the dactinomycin content as follows:

(i) *Sample solution.* Reconstitute the vial with 2.0 milliliters of mobile phase. Shake well and filter if necessary.

(ii) *Calculations.* Calculate the dactinomycin content of the vial as follows:

$$\text{Milligrams of dactinomycin per vial} = \frac{A_u \times P_s \times d}{A_s \times 500}$$

where:

A_u=Area of the dactinomycin peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s=Area of the dactinomycin peak in the chromatogram of the dactinomycin working standard;

P_s=Dactinomycin activity in the dactinomycin working standard solution in micrograms per milliliter; and

d=Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except use the entire contents of each of the immediate containers tested.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, preparing the

sample for test as follows: Use a sufficient number of containers to yield 3 milligrams of dactinomycin. Reconstitute by adding 1.1 milliliters of sterile water for injection to each container. Aseptically pool the resultant solutions from each container. Dilute an accurately measured portion with sufficient diluent 1 to give a concentration of 0.2 milligram of dactinomycin per milliliter.

(4) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(5) *pH.* Reconstitute as directed in the labeling and proceed as directed in § 436.202 of this chapter.

[39 FR 19145, May 30, 1974, as amended at 44 FR 10379, Feb. 20, 1979; 46 FR 16685, Mar. 13, 1981; 46 FR 46313, Sept. 18, 1981; 49 FR 6093, Feb. 17, 1984; 49 FR 15074, Apr. 17, 1984; 49 FR 24018, June 11, 1984; 50 FR 1504, Jan. 11, 1985; 50 FR 19676, May 10, 1985]

§ 450.222 Daunorubicin hydrochloride for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Daunorubicin hydrochloride for injection is a freeze-dried powder whose components are daunorubicin hydrochloride and mannitol. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of daunorubicin that it is represented to contain. It is sterile. It is nonpyrogenic. It contains no depressor substances. Its moisture content is not more than 3.0 percent. When reconstituted as directed in the labeling, its pH is not less than 4.5 and not more than 6.5. It passes the identity test. The daunorubicin hydrochloride used conforms to the standards prescribed by § 450.22(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The daunorubicin hydrochloride used in making the batch for potency, moisture, pH, crystallinity, and identity.

(*b*) The batch for potency, sterility, pyrogens, depressor substances, moisture, pH, and identity.

(ii) Samples required:

(*a*) The daunorubicin hydrochloride used in making the batch: 14 packages, each containing approximately 40 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 34 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay.* Daunorubicin hydrochloride is toxic. It must be handled with care in the laboratory. Solutions should not be pipetted by mouth. Transfer all dry powders in a suitable hood. Wear rubber gloves, protective gowns, head coverings, and protective eye goggles when handling dry powders. If the substance contacts the skin, wash with soap and water. Dispose of all waste material by dilution with larger volumes of sodium hypochlorite solution.

(1) *Daunorubicin content (high-pressure liquid chromatography).* Proceed as directed in § 436.322 of this chapter, preparing the sample and standard solutions and calculating the daunorubicin content as follows:

(i) *Preparation of working standard solution.* Accurately weigh approximately 25 milligrams of the daunorubicin working standard and dissolve in 25 milliliters of the internal standard solution prepared as directed in § 436.322(b)(3) of this chapter.

(ii) *Preparation of sample solution.* Prepare the sample solution by rinsing the contents of the vial into an appropriate-sized volumetric flask with a sufficient amount of internal standard solution prepared as directed in § 436.322(b)(3) of this chapter, to obtain a concentration of 1.0 milligram of daunorubicin per milliliter.

(iii) *Calculations.* Calculate the daunorubicin content as follows:

$$\text{Daunorubicin content per vial in milligrams} = \frac{R_u \times W_s \times V \times P}{R_s \times 25 \times 1{,}000}$$

where: